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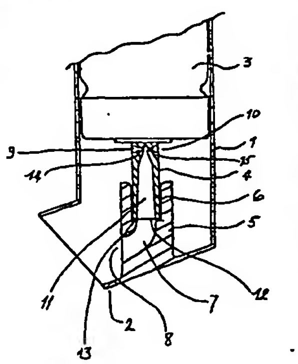

(57) Abstract: An aerosol inhalation device, comprises an actuator (1), a canister (3) containing pressurized aerosol formulation received in said actuator, the canister having a dispensing metering valve comprising a metering chamber, a valve stem (4) disposed therein and movable between a charge position, in which the chamber is isolated from the atmosphere whilst the chamber communicates with the interior of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister (3). The valve stem (4) has at least one transfer port (9, 10), adapted to communicate with the chamber in the discharge position and a discharge port (12), adapted to engage valve stem location means (5) in the actuator (1) having a flow connection with the atmosphere. The stem (4) includes a flow conduit (11) linking the at least one transfer port (9, 10) with the discharge port (13), such that the valve stem and the valve stem location means (5) cooperate to form a continuous flow path (7, 11), characterised in that the stem (4) includes spray-producing means (14, 15).

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IMPROVED METERING VALVE AND ACTUATOR FOR METERED DOSE INHALER

The present invention relates to a metered dose inhaler for delivering a metered amount of a formulation from a pressurized canister carrying a metering valve in which spray producing means are located in the metering valve, in particular in the valve stem of the metering valve, rather than in the actuator.

Portable devices are widely available to a patients wishing to self-administer therapeutic and preventative medicament formulations to combat the symptoms of respiratory disorders, such as asthma. Such devices are generally arranged to dispense a discrete amount of the formulation, (usually in the form of a fluid or particulate medicament entrained in a stream of gas or vapour) into the respiratory passages and are widely referred to as metered dose inhalers.

Typically, a metered dose inhaler comprises two main parts, namely a canister containing the pressurized formulation and an actuator device having a mouth piece for delivering the metered amount of formulation to the user.

In general, a metered dose inhaler comprises a cylindrical housing which receives a cylindrical canister containing a pressurized medicament formulation. The canister is provided with a dispensing metering valve including a metering chamber and a valve stem having an internal conduit which makes a tight push fit engagement into a valve stem block located towards the end portion of the cylindrical housing and adjacent the mouth piece situated at the end of the actuator.

To actuate the metered dose inhaler, the user applies a compressive force to the closed end of the canister. The internal components of the metering

valve are spring-loaded so that a low compressive force is sufficient for the canister to move axially with respect to the valve stem by an amount sufficient for the valve stem to penetrate the canister and cause a metered quantity of formulation to be expelled through a single transfer port (of diameter about 0.6mm) into the internal conduit of the valve stem which communicates with an internal cavity in the valve stem block which generally includes a large sump. The formulation flows from the sump via a channel into a cone-shaped spray nozzle situated in the valve stem block and thereafter into the mouth piece of the actuator, whereby a user inhaling through the mouth piece will receive a metered dose of medicament containing formulation. There is therefore defined a non-uniform flow path of large volume between the discharge port of valve stem and the mouth piece. In particular, it should be noted that the valve stem block contains a spray-producing means in the form of the conical nozzle (I).

When a metered dose inhaler is operated in this manner, the propellant formulation undergoes rapid initial expansion at atmospheric pressure into the relatively large volume of the internal cavities of the valve stem end of the valve stem block to produce a range of different sizes of propellant droplets containing the medicament either in suspension or in solution. Although the number of large droplets decreases over time, the user tends to inhale a mixture of small and large droplets. Whilst small droplets tend to exert the desired therapeutic effect, large droplets are known to deposit undesirably in certain bodily regions where they may lead to localized side effects. Similar considerations apply in relation to dry powder metered dose inhalers where there is a risk that larger powder particles will deposit in the upper air ways, rather than the fine branches of the lung, undesirable bodily regions.

In order to alleviate this effect, the diameter of the channel linked to the spray nozzle in conventional metered dose inhalers is generally low enough to create a constriction or bottleneck in the non-uniform flow path. Typically, the channel is 0.22mm or less in diameter so as to impose primary

flow control and prevent the undesirable accumulation of larger droplets/particles. This narrow channel has the added benefit that the droplets/particles do not pass too quickly into the users mouth.

A disadvantage of imposing primary flow control in this manner is that the channel is prone to blockage. For example, it has been found that in dispensing Salbutamol HFA (which is a suspension of Salbutamol in P134a containing about 10% ethanol) the medicament accumulates at or near to the entrance and exit end of the channel. As well as the inconvenience to the user, the build-up of material leads to a reduction in the effective dose dispensed. This effective dose can drop significantly over the lifetime of the metered dose inhaler (typically 200 to 300 doses).

The present invention seeks to improve delivery of a pressurized formulation from a metered dose inhaler by locating spray-producing means in the flow path at or near to the outlet of the pressurized canister, rather than in the actuator. More particularly, the spray-producing means are located at or near to the outlet of the pressurized canister by having spray-producing means, e.g. in the form of a spray orifice, in the valve stem. The advantage to the user is that a softer spray of a formulation of improved quality is achievable without increasing the risk of blockage.

According to the invention, there is provided an aerosol inhalation device, comprising an actuator, canister containing pressurized aerosol formulation received in said actuator, the canister having a dispensing metering valve comprising a metering chamber, a valve stem disposed therein and movable between a charge position, in which the chamber is isolated from the atmosphere whilst the chamber communicates with the interior of the canister, and a discharge position, in which the contents of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister, the valve stem having at least one transfer port, adapted to communicate with the chamber in the discharge position and a discharge port, adapted to engage valve stem location means in the actuator having a

flow connection with the atmosphere, the stem including a flow conduit linking the at least one transfer port with the discharge port, such that the valve stem and the valve stem location means cooperate to form a continuous flow path, characterized in that the stem includes spray-producing means.

Although the introduction of spray-producing means into the valve stem might have been expected to allow the formulation to exhaust more rapidly and therefore to add to the problems of blocking etc., it has been found that that this is not so. A spray orifice located in the flow path at or near to the exit end of the pressurized canister eliminates the need for a narrow diameter channel in the valve stem block and permits a larger diameter discharge aperture in the vlave stem block than might otherwise been have expected for this type of arrangement.

The spray-producing means may be in the form of a spray orifice located close to the transfer port of the valve stem, and in the flow path defined by the valve stem and the valve stem location means. In such an arrangement, the one or more transfer ports in the valve stem communicate with the spray orifice by means of a spray channel of substantially smaller diameter to the internal flow conduit of the valve stem. This channel may be, for example, less than 0.3mm, such as 0.2mm in diameter, so as to break up the pressurized liquid formulation into droplets. The valve stem may be provided with more than one transfer port, eg. two, substantially diametrically opposed to one another. Preferably, when there is more than one aperture, the apertures are arranged in a substantially common radial plane of the valve stem. If there are more than two transfer ports, they are preferably arranged symmetrically so that the flow of formulation (which may be suspended or dissolved in the liquefied propellant) is effectively in the center of the flow path of the valve stem.

When the spray-producing means are located in the valve stem and separate form the transfer ports, the external aperture size transfer ports may be of conventional dimensions, (e.g. having a diameter of about 0.6mm).

In an alternative embodiment, a transfer port may act as the spray-producing means, provided that it is sufficiently small to restrict the flow of formulation from the pressurized canister.

When more than one transfer port acts as the spray-producing means, there are preferably at least two transfer ports arranged in a substantially common radial plane of the valve stem. In this alternative embodiment, there are preferably two transfer ports substantially diametrically opposed to one another. If there are more than two transfer ports, they are preferably arranged symmetrically so that the flow of formulation is mixed in the center of the flow conduit of the stem.

Preferably, the internal conduit of the valve stem tapers uniformly and inwardly from the end portion bearing the discharge port to the portion bearing the transfer port, for ease of moulding. In this embodiment, the internal conduit may be essentially conical (e.g. a truncated cone). The diameter of the outermost bore (y) is preferably between x and 10x (where x is the diameter of the innermost bore).

Preferably, the diameter of the innermost bore (x) is 80% or less of the diameter of the outermost bore (y). Particularly preferably, the diameter of the innermost bore (x) is in the range of 40 to 80% of the diameter of the outermost bore (y).

Typically, when the transfer ports in the valve stem function as the spray-producing means they have a diameter of 0.12mm or more. In general, effect sprays are produced when the diameter is less than 0.4mm.

Typically, the valve stem location means is in the form of a valve stem block provided with a valve stem location portion, in which the valve stem makes a tight fit engagement and a dispensing portion, which is arranged to dispense atomized formulation to the user.

Typically, the valve stem engagement portion and the discharge portion are linked by a flow path which has a diameter greater than 0.22mm, (for example, 0.5-2mm).

The flow channel in the valve stem location means may form an L-shaped flow path with the valve stem. In general, the two limbs of such an L-shaped flow path are at an angle of greater than 90°, e.g. about 115°. However, the two limbs of the flow path may be at an angle as great as 135° or more. The flow path defined by the valve stem and the valve location means need not be angled, and it is possible to have the flow path defined by the valve stem location means which is straight line.

Preferably the cavity in the valve stem contains a shoulder upon which a portion of the wall at the first end of the valve stem is supported. Preferably the supported portion of the wall at the first end of the valve stem is a portion farthest away from the spray producing means.

Preferably the actuator device is provided with a delivery outlet adapted to deliver the discrete amount of formulation to the user, said delivery outlet being in fluid communication with the dispensing portion of the valve stem location means. The outlet may be adapted for nasal delivery or preferably, with a mouthpiece for oral delivery to the lungs, via the pharynx.

The dispensing portion of the valve stem location means may take any convenient shape such as a V-shape. In order to prevent rapid expansion and solid deposition on the walls of the dispensing portion, alternative shapes may be used such as W-shapes. Preferably the dispensing portion has curved internal walls to define a smooth flow path.

According to a further aspect of the invention, we further provide a valve stem as hereinbefore defined.

According to the invention, we further provide an actuator for use in association with a pressurized container having a metering valve as hereinbefore defined. Preferably, the actuator comprises a valve stem location means capable of engaging a valve stem of a pressurised container such that the valve stem and the valve stem location means cooperate to form a continuous flow path.

In general, the methods for manufacturing the components parts of the invention will be familiar to those skilled in the art. For example, injection moulding may be used to make the valve stem. In general, the internal conduit of the valve stem will be larger than the internal conduit of conventional valve stems of this invention. When the spray-producing means is combined with the transfer ports, the internal conduits of the transfer ports will generally be smaller relative to those described in the prior art, which will necessitate the use of smaller diameter side pins. In contrast, the moulding stem pin will generally be larger than used relative to the prior art. During injection, two supporting side pins may be used to grip the stem pin whilst forming twin apertures. The stem and side pins are made from any suitable material such as steel.

The metered dose inhaler of the invention may be of the manually operable or breath actuated type. It is envisaged that the invention may be used primarily in conjunction with the delivery of a medicament in the form of a propellant solution, dispersion or (preferably) suspension or in the form of a dry powder. It is thought that pulmonary inhalation would be the primary application of the invention either nasally or (preferably) orally and the delivery outlet of the actuator device may be adapted accordingly.

By way of example only, the present invention could be used to deliver medicaments including antiallergics, analgetics, bronchodilators, antihistamines, therapeutic proteins and peptides, antitussives, anginal preparations, antibiotics, anti-inflammatory preparations, hormones, or sulfonamides (such as for example a vasoconstrictive amine, an enzyme, an

alkaloid, or a steroid and synergistic combinations of these). Examples of medicaments which may be employed are: Isoproterenol [alpha (isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, flumisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, and dismorphine. Others are antibiotics (such as neomycin, streptomycin, penicillin, procaine penicillin, tetracycline, chlorotetracycline and hydroxytetracycline), adrenocorticotropic hormones and adrenocortical hormones (such as cortisone, hydrocortisone, hydrocortisone acetate and prednisolone), insulin and antiallergy compounds (such as cromolyn sodium).

In a preferred embodiment of the metered dose inhaler of the invention, the formulation comprises: salbutamol together with a propellant and optionally one or more additives. Particularly preferably the formulation comprises salbutamol and P134a (especially preferably with about 10wt% ethanol).

Preferred embodiments of the device according to the invention will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 is a partially truncated vertical section of an aerosol actuator according to the invention fitted with a pressurized medicament canister;

Figure 2 is a metering valve according to the invention, shown in vertical section and;

Figure 3 are alternative embodiments of valve stems according to the invention, shown in partially truncated vertical section.

Referring first to Figure 1, an aerosol inhalation actuator comprises a

generally cylindrical housing (1) having a mouth piece (2) angled at about 115° to the perpendicular axis of the cylindrical housing (1). The housing (1) receives a cylindrical canister (3) of pressurized medicament, the canister (3) being provided at one end with a metering valve including a valve stem (4). The valve stem (4) is located in, by means of a tight fit engagement, in a cavity in a valve stem location means in the form of a valve stem block (5) extending upwardly from the closed base of the cylindrical housing (1). In addition to a reception cavity (6), which engages with the valve stem (4), the valve stem block (5) encloses a channel (7) communicating with the reception cavity (6) and terminating in a discharge exit opposite the mouth piece (2), such that the valve stem (4) and the valve stem block (5) cooperate to form a generally L-shaped continuous flow path. The discharge exit (8) of channel (7) is tapers outwards with respect to the overall cross-section of channel (7), and typically is of a diameter in the range 0.5-2mm.

Valve stem (4) has a substantially cylindrical main body with a pair of diametrically disposed transfer ports (9,10) located adjacent to and just outside the canister (3), when the canister is in the charge position. The valve stem (4) encloses a uniformly tapering internal conduit (11) extending, at its narrow end, from the region of the transfer ports (9,10) and terminating with the discharge port (12) of the valve stem, which is located in the valve stem block (5). The discarge end portion of the valve stem (4) is partially seated on an internal shoulder (13) in the reception cavity (6).

The transfer ports (9,10) are in the form of cylindrical apertures in the outer surface of the valve stem (4), each transfer port after an initially cylindrical cross-section tapers down to cylindrical channels (14,15) in moving towards the center of the valve stem, the ports (9,10) and channels (14,15) acting as a spray-producing means in the form of opposed spray orifices. The ports (9,10) channels (14,15) internal conduit (11) and stem block channel (7) cooperate to form a continuous flow path.

Axial movement of the canister (3) relative to the valve stem 4 and towards

the stem block (5) permits transfer ports (9,10) to enter the metering valve in the canister (3). A metered amount of pressurized formulation passes through ports (9,10) and into the innermost ends of the channels (14,15) in the valve stem (4). The two streams of formulation are atomized and interfere to such an extent that the combined flow is slowed relative to its initial velocity. The formulation passes out of the discharge exit (8) in the valve stem block and delivers the formulation through the mouth piece (2) to the user.

Referring now to Figure 2, a metering valve according to the invention comprises a body in the form of a circular cup (21) fitted in a ferrule (22). A valve bush (23) provided with an aperture base fits in the cup (21) defining a metering chamber (24) which is fixed with respect to the cup (21). The metering chamber (24) is provided at the outer end, immediately adjacent to the field (22) with an outer seal or gasket (25), and at the inner end with an inner seal or gasket (26). The inner end of the chamber (24) is adapted to fit within the interior of a pressurized aerosol canister.

A hollow tubular guide (27) extends from the cup 20 beneath the chamber (24) and inner seal (26). The side walls of the guide (27) are additionally provided with diametrically opposed elongate apertures (not shown). The lower end portion of the guide (27) is provided with an inwardly facing peripheral flange (28).

A valve member in the form of a valve stem (29) of generally circular cross-section extends through the chamber (24) and into the interior of the guide (27). The end portion of the valve stem extending into the guide (27) is surrounded by a compression spring (30), retained in the guide (27) by the flange (28), and bearing against an annular collar (31) mounted on the inner end portion of the valve stem (29). The collar (31) is slidably mounted within the guide (27).

The spring (30) urges the valve stem (29) towards the inoperative position

shown in Figure 2. The outwards movement of the valve stem (29) is limited by a peripheral rib (32) extending from the stem (29) within the metering chamber (24), which bears against the outer seal (25) when the valve is in the inoperative position. The rib (32) also limits the inwards movement of the valve stem (29) by bearing against the base of the bush (23) when the valve stem is in the operative (discharge) position.

The lower portion of the valve stem (29) is provided with means for the communicating the chamber (24) with the interior in the form of a plurality of channels (33) when the valve stem (29) is in the inoperative position. The channels (33) are arranged such that when the stem (29) is in the inoperative position, they terminate just above the inner seal (26), within the base of the bush (23). A small annular space, (34), e.g. of about 0.2mm width, provided in the base of the bush (23) and surrounding the valve member (29), ensures the communication between the chamber (24) and the interior is established by the channels (33) when the valve stem (29) is in the inoperative position.

The outer end portion of the valve stem (29) is provided with an outlet conduit (35) through which a charge can be dispensed from the metering chamber (24), such charge entering the outlet conduit (35) through diametrically opposed transfer ports (36, 37) located on the valve stem (29) and lying outside the metering chamber (24) when the valve is in the inoperative (charge) position (as shown). The entrance of the transfer ports in the outer wall of the valve stem (29) are cylindrical in cross-section, but on moving towards the center of the valve stem taper towards spray channels (38, 39) which, with the tapered portion of the transfer ports (36, 37) function as spray-producing means. The transfer ports (36, 37), channels (38, 39), and internal conduit (35) form a continuous flow path through which a charge can be dispensed from the metering chamber (24), such charge entering the outlet conduit (35) via the transfer ports (36, 37). In the inoperative (charge) position, the transfer ports lie outside the ferrule (22), and communicate with the chamber (24), on inward movement of the stem

(29) to the operative (discharge) position.

The stem (29) forms a sealing fit with the outer seal (25) in both the operative and inoperative positions, and a sealing fit with inner seal (26) only when the valve is in the operative position.

Thus, in the inoperative position, the chamber (24) is sealed from the outside (the atmosphere), but is adapted to communicate with the interior of the container, and in the operative position communicates with the outside, while being sealed from the interior.

In use, the valve is crimped onto a cylindrical canister for pressurized aerosol material, eg a medicament formulation, the container bearing against the container gasket (40). In the inoperative position, the pressurized material can readily move from the chamber (24) to the interior of the container, and vice versa, by means of the channels (33).

With the valve inverted, ie with the outer dispensing portion of the valve stem (29) pointing downwards, the chamber fills with pressurized liquid propellant. Actuation of the valve stem (29), against the bias of the spring (30), causes the transfer ports (36, 37) to move into the chamber (24), allowing pressurized material to be dispensed from the chamber (24) via the internal conduit (35) to the outside.

In Figure 3, alternative embodiments of the valve stem are illustrated. In Figure 3(a), a valve stem (51) is provided with an internal conduit (52) connecting the discharge end of the stem (53) with a transfer port (54)

radially disposed towards the opposing end of the stem. A spray nozzle formed from a cylindrical channel (55) disposed on the vertical axis of the valve stem and a cone (56) communicate with the transfer port (54) and the internal conduit (52) to form a continuous flow path.

Figure 3(b) illustrates a valve which is similar to that illustrated in Figure 3(a) save that two transfer ports (57, 58) are diametrically disposed across a valve stem (59), to form a single through going channel. A spray nozzle formed from a cylindrical channel (60) disposed on the vertical axis of the valve stem and a cone (61) communicate with the transfer port (54) and the internal conduit (52) to form a continuous flow path.

Figure 3(c) is a vertical section through the valve stem of Figure 3A along the lines I-I.

In figure 3(d), spray-producing means are formed in a valve stem (62) having an internal conduit (63), by having radially disposed transfer ports (64, 65) which intersect with the non-discharge portion of the internal conduit. In use, a metered amount of formulation passes through transfer ports (64.65) into the innermost end of the tapered internal conduit (63) of the valve stem(62). The two streams of formulation interfere to such as extent that a spray is produced in the region of the non-discharge portion (66) of the conduit (63).

Claims

1. An aerosol inhalation device, comprising an actuator (1), a canister (3) containing pressurized aerosol formulation received in said actuator, the canister having a dispensing metering valve comprising a metering chamber, a valve stem (4) disposed therein and movable between a charge position, in which the chamber is isolated from the atmosphere whilst the chamber communicates with the interior of the canister (3), and a discharge position, in which the contents of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister (3), the valve stem (4) having at least one transfer port (9, 10), adapted to communicate with the chamber in the discharge position and a discharge port (12), adapted to engage valve stem location means (5) in the actuator (1) having a flow connection with the atmosphere, the stem including a flow conduit (11) linking the at least one transfer port (9, 10) with the discharge port (13), such that the valve stem and the valve stem location means cooperate to form a continuous flow path (7, 11), characterized in that the stem (4) includes spray-producing means (14, 15).

2. A device according to Claim, wherein the stem (4) is provided with more than one transfer ports (9, 10).

3. A device according to Claim 1 or Claim 2, having two transfer ports (9, 10) substantially diametrically opposed to one another.

4. A device according to any one of the preceding Claims, in which the spray producing means (14, 15) are separated from the transfer ports (9, 10).

5. A device according to any one of Claims 1 to 3, wherein the transfer ports (63, 65) act as the spray producing means.

6. An inhalation actuator (1) for use with a canister (3) containing a pressurised aerosol formulation, the actuator (1) being adapted to receive canister (3), the canister (3) having a dispensing metering valve comprising a metering chamber, a valve stem (4) disposed therein and movable between a charge position, in which the chamber is isolated from the atmosphere whilst the chamber communicates with the interior of the canister, and a discharge position, in which the contents of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister, the valve stem (4) having at least one transfer port (9, 10), adapted to communicate with the chamber in the discharge position and a discharge port (12), adapted to engage valve stem location means (5) in the actuator (1) having a flow connection with the atmosphere, the stem including a flow conduit linking the at least one transfer port (9, 10) and the discharge port (12), such that the valve stem (4) and the valve stem location means (5) cooperate to form a continuous flow path, characterised in that the stem (4) includes spray producing means (14, 15).

7. A canister (3) containing a pressurised aerosol formulation, for use with an inhalation actuator(1) adapted to receive the canister (3), the canister (3) having a dispensing metering valve comprising a metering chamber, a valve stem (4) disposed therein and movable between a charge position, in which the chamber is isolated from the atmosphere whilst the chamber communicates with the interior of the canister, and a discharge position, in which the contents of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister, the valve stem (4) having at least one transfer port (9, 10), adapted to communicate with the chamber in the discharge position and a discharge port (12), adapted to engage valve stem location means (5) in the actuator (1) having a flow connection with the atmosphere, the stem (4) including a flow conduit linking the at least one transfer port (9, 10) and the discharge port (12), such that the valve stem (4) and the valve stem location means (5) cooperate to form a continuous flow path (7, 11), characterised in that the stem (4) includes spray producing means (14, 15).

8. An aerosol dispensing metering valve, for use with a canister containing pressurised aerosol formulation, comprising a metering chamber (24), a valve stem (29) disposed therein and movable between a charge position, in which the chamber (24) is isolated from the atmosphere whilst the chamber (24) is adapted to communicate with the interior of the canister, and a discharge position, in which the contents of the chamber can be discharged to the atmosphere whilst the chamber is isolated from the canister, the valve stem having at least one transfer port (36, 37), adapted to communicate with the chamber (24) in the discharge position and a discharge port (35), the stem (29) including a flow conduit linking the at least one transfer port (36, 37) and the discharge port (35), characterised in that the stem (29) includes spray producing means (36, 37).

Figure 1

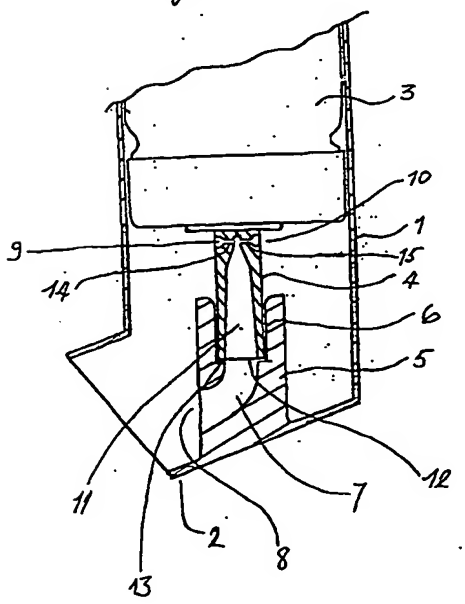


Figure 2

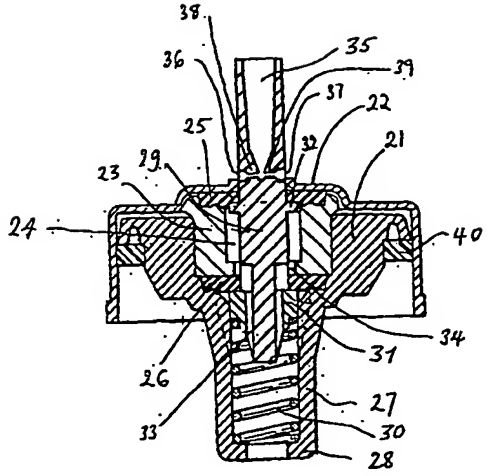
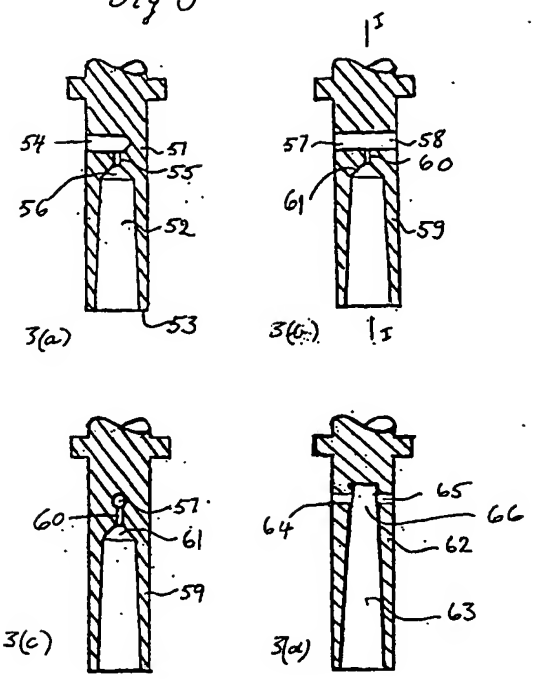


Fig 3



INTERNATIONAL SEARCH REPORT

PCT/GB 01/05297

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00 B65D83/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y		3,7
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2002	26/03/2002
Name and mailing address of the ISA: European Patent Office, P.B. 5818 Patentlaan 2, NL - 2280 HV Rijswijk, Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer: Valfort, C

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A	EP 0 692 434 A (V A R I S P A) 17 January 1996 (1996-01-17) column 3, line 20 -column 3, line 24; figure 1	2-5

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